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Original Research

Impact of prognostic factors on platinum response in extrapulmonary neuroendocrine carcinoma

Neuroendocrine carcinoma

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Abstract

Aim: Extrapulmonary neuroendocrine carcinomas are rare tumors and clinical trials for their treatment are limited. In this study, we aimed to determine the impact of clinicopathological and prognostic factors on platinum response in patients diagnosed with advanced EP-NECs.

Material and Methods: Patients diagnosed with extrapulmonary neuroendocrine carcinoma were included in the study. General characteristics and response rates were saved. Univariate and multivariate analyses were used to determine prognostic factors. We divided patients into three groups: pancreatic, gastrointestinal and other extrapulmonary primary. Progression-free survivals were compared to each other.

Results: We analyzed 37 patients in our study. The median age was 60 in our study. The most frequent primary origin of neuroendocrine carcinoma was the pancreas. Liver metastases were correlated with poor progression-free survival. Overall response rate was achieved in 26 patients (70%). PFS was 6 months in all groups and 4 for gastrointestinal, 8 for pancreatic, 9 months for other extrapulmonary NECs (p=0.37).

Discussion: Due to the rare incidence of the disease, few randomized controlled trials have been conducted. These treatment recommendations are extrapolated from small cell lung cancer trials. Most of the patients diagnosed with advanced extrapulmonary neuroendocrine carcinomas responded to platinum-based therapy. Liver metastasis was a poor prognostic factor for progression-free survival.

Keywords

Extrapulmonary, Neuroendocrine Carcinoma, Prognostic Factors

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Introduction

Neuroendocrine neoplasms are not a homogenous group. They include well and poorly differentiated groups. Well differentiated group includes neuroendocrine tumor, poorly differentiated group includes neuroendocrine carcinoma [1]. Neuroendocrine carcinomas are rare tumors and they originate mostly from lungs. Approximately 10% of neuroendocrine carcinomas originate from extrapulmonary origin [2]. Thus, these are rare tumors for which not enough clinical trials have been conducted [3,4]. Because there is a similarity in immunohistochemistry and fast-growing behavior between NEC and small cell lung cancer, it is recommended that NEC patients are treated similarly to small cell lung cancer [5].

Extrapulmonary neuroendocrine carcinomas (EP-NEC) are mostly metastatic at initial diagnosis [6]. For patients who are not amenable to curative surgery, platinum /etoposide chemotherapy is the preffered regimen [3,4]. Some studies had shown the efficacy of this regimen, but this efficacy was short lived. There have been few studies in the literature regarding EP-NEC and its treatment. Therefore, EP-NEC had many unknown characteristics that needed to be investigated.

In this study, we aimed to determine the impact of clinicopathological and prognostic factors on platinum response in patients diagnosed with advanced EP-NECs

Material and Methods

All patients diagnosed with advanced extrapulmonary neuroendocrine carcinoma and received platinum-based chemotherapy at Kayseri City Education and Research Hospital and Erciyes University Medical Faculty were retrospectively reviewed. We excluded patients diagnosed with mixed adenoneuroendocrine carcinomas and local/local advanced neuroendocrine carcinomas from the study.

Data collected from the hospital patient records included patient characteristics, primary tumor location, chemotherapy regimens given to patients, chemotherapy responses, ki67 levels, metastatic sites, number of metastatic sites, and the date of death.

We divided patients into three groups: pancreatic, gastrointestinal and other extrapulmonary origin. Response rates were saved. Univariate and multivariate analyses were used to determine prognostic factors on progression-free survival of platinum therapy in advanced extrapulmonary neuroendocrine carcinoma, and progression-free survivals were analysed for these groups.

The present study was approved by the ethics committee of Kayseri City Hospital (721-2022-10-25).

Statistics

Median, min, max and frequencies were defined. The Kaplan-Meier method and log-rank test were used to analyze progression-free survival (PFS). PFS was defined as the time from first platinum-based chemotherapy to progression or death. A p-value <0.05 was considered statistically significant. The Cox proportional hazards model was used for the univariate and multivariate analyses. The response was evaluated as com¬plete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Results

Patients and characteristics

Fourty-five patients diagnosed with extrapulmonary neuroendocrine carcinoma were retrospectively reviewed. Among these patients, we excluded 8 patients from the study because three of them died before treatment, and 5 of them

Table 1. General Characteristics and overall response rate of advanced extrapulmonary NEC.

Characteristics		N=37	Overall response rate
Age years, min-max		60 (18-79)	
Age	≥65	11 (30%)	55
	<65	26 (70%)	77
Gender	Male	25 (68%)	76
	Female	12 (32%)	58
Ki67			
<55		13 (35%)	54
≥55		24 (65%)	79
Primary Site			
Gastrointestinal		12 (32.4%)	75
Pancreas		13 (35.1%)	69
Other		12 (32.4%)	67
Bladder		4	
Cutaneous		3	
Ovarian		1	
Bile Duct		1	
Larynx		1	
Prostat		1	
Unknown primary		1	
Surgery			
Yes		13(35%)	
Curative		6	
Palliative		7	
No		24 (65%)	
Metastatic site			
Liver		22 (59%)	
Lung		6 (16%)	
Bone		8 (22%)	
Peritoneum		3 (8%)	64
Brain		1 (3%)	
Surrenal		2 (5%)	
Lymp node		7 (19%)	
Number of metastatic site			
1		28 (76%)	65
2 and upper		9 (24%)	80
Platinum chemotherapy			
Cisplatin-etoposide		30	
Carboplatin-etoposide		5	
Carboplatin-paclitaxel		1	
Lipoplatin-etoposide		1	
Platinum chemotherapy line			
First line		32 (86%)	
Second line		5 (14%)	
Best Response to platinum Chemotherapy			
Partial/Complete Response		22 (59 %)	
Stable disease		4 (11%)	
Progressive disease		11 (30%)	

were not at an advanced stage. We analyzed 37 patients in our study.

The median age was 60 (18-79) years in our study. Twelve of them (32%) were female, 25 of them (68%) were male; 26 of them (70%) were under 65 years of age. Ki67 levels of thirteen patients (35%) were under 55. The primary origin of neuroendocrine carcinoma was the pancreas in thirteen of patients (35.1%), gastrointestinal system in 12 patients (32.4%) and the other sites in 12 patients (32.4%). Other sites were bladder with 5 patients, cutaneous with 3 patients, ovarian, bile duct, larynx and unknown primary with one patient each other. Twenty-two patients had liver metastasis (59%). All characteristics are shown in Table 1.

Table 2. Univariate and multivariate Cox regression analyses for platinum-based progression-free survival in patients diagnosed with extrapulmonary neuroendocrine carcinoma.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender Male vs Female	1.186 (0.552-2.549)	0.662		
Age (<65 or ≥65)	2.194 (0.981-4.903)	0.056	1.651 (0711-3.836)	0.243
Ki67 score (<55 or ≥55)	1,306 (0.616-2.767)	0.487		
Primary				
-Gastrointestinal		0.430		
-Pancreas	0.555 (0.229-1.349)	0.194		
-Other	0.743 (0.295-1.873)	0.529		
Primary (Other or Gastroenteropancreatic)	0.954 (0.429-2.122)	0.909		
Metastatic site 1 vs ≥2	0.601 (0.269-1.340)	0.213		
Liver metastasis No vs Yes	2.649 (1.187-5.912)	0.017	0.433 (0.188-0.995)	0.049
NSE level High vs not	0.770 (0.349-1.700)	0.518		

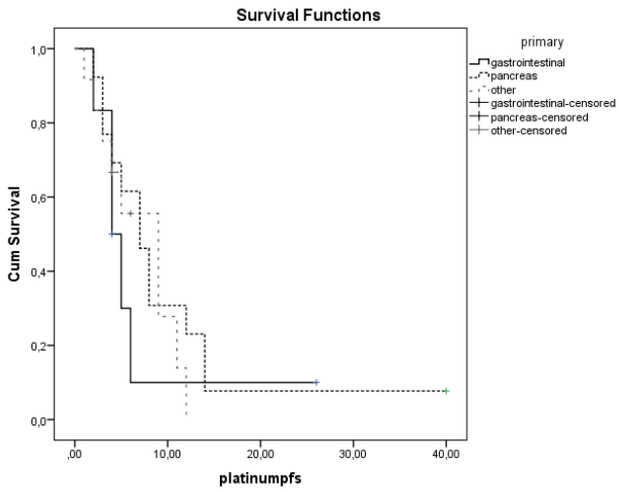

Figure 1. Progression-free survival of gastrointestinal, pancreas and other extrapulmonary neuroendocrine carcinomas on platinum-based therapy.

The univariate analyses revealed that only liver metastasis (95% CI 2.649 p: 0. 017) was correlated with poor progression-free survival in patients who were treated with platinum-based therapy diagnosed with extrapulmonary neuroendocrine carcinoma. The equal and older 65 years correlated with poor prognosis but it did not meet statistical significance in univariate analyses (95% CI 2.194 p:0.056).

Multivariate analyses revealed that liver metastasis correlated with poor overall survival with a hazard ratio of 0.433 (0.188-0.995) (p=0.049)

Response and Survival

The overall repsonse rate was achieved in 26 patients (70%). One patient had a complete response, twenty-two patients had a partial response (59%), four patients (11%) had stable disease (Table 1).

PFS was 6 (3.81-8.18) months. PFS was 4 (2.40- 5.59) months for gastrointestinal NEC, 8 (4.87-11.12) months for pancreatic NEC, 9 (4.53-13.46) months for other extrapulmonary NECs. There was no significant difference in primary origin (p=0.37).

Discussion

In this study, we evaluated general characteristics and prognostic factors that affect platinum response in extrapulmonary NEC patients. The standard treatment of extrapulmonary neuroendocrine carcinoma is platinum-based agents. Due to the rare incidence of the disease, few randomized controlled trials have been conducted. These treatment recommendations are extrapolated from small-cell lung cancer trials [7].

Neuroendocrine carcinomas occur in all parts of the body. Dasari et al reported from a SEER database that extrapulmonary neuroendocrine carcinomas most commonly originate from the gastrointestinal tract with 37%. The second most common primary origin was unknown primary with 28% [6]. In a study from Sorbye et al, they reported that the most common primary site was gastrointestinal, second most common site was the pancreas [8]. In our study, the most common site of primary lesion was the pancreas. Gastrointestinal tract was the second most common primary origin of EP-NEC.

In our study, the overall response rate was 70%, and the objective response rate was 59% and the progression-free survival of platinum therapy was 6 months in all EP-NEC.

Iwasa et al. reported that the overall response rate in patients who received first-line platinum and etoposide-diagnosed neuroendocrine carcinoma of the hepatobiliary tract and pancreas was 62%. There was no complete response. The median progression-free survival was 1.8 months in this trial. In this trial, there was only NEC-originated hepato-biliary-pancreas [9]. In our study, there are not only pancreatic NECs, but also gastrointestinal and other extrapulmonary NECs. Our overall response rate and progression-free survival are better than in this study. Our better results may be associated with relatively low prevalence of liver metastasis and peritoneal dissemination. Liver metastases were present in 81% of patients, and peritoneal dissemination was present in 52% of patients. In a study by Brandi et al., they found outcomes similar to our study. They found that the response rate of the platinum therapy was 52% and PFS was 7 months. As in our study, the most common primary site of NEC was the pancreas with (24%)

[10]. The progression-free survival according to the primary site is shorter in the gastrointestinal tract (4 months) than in pancreas (8 months) and other EP-NEC (9 months) in our study. But there was no significant difference. In a previously reported study, tprogression free survival for first- line platinum-based chemotherapy was 5 months for pancreatic NEC, 3-7 months for gastrointestinal NEC [8].

In our study, 59% of patients had liver metastasis. We demonstrated that liver metastasis is significantly associated with poor progression-free survival on platinum-based chemotherapy. Liver metastasis is well-known poor prognostic factor in neuroendocrine tumor [11,12,13]. Progression-free survival of other than gastroenteropancreatic neuroendocrine carcinomas is longer than for gastroenteropnacreatic neuroendocrine carcinomas, although this is not significant. This may be due to the fact that gastroenteropancreatic NECs have much more liver metastases than the other primary sites. In univariate analyses, ki67 level under or upper 55 we did not demonstrate statistically significant prognostic parameters for progression free survival on platinum based therapy in our study. A previous study demonstrated that the ki67 level is a prognostic marker [14]. But another study demonstrated that the chemotherapy response is lower in patients that had ki67 below 55% than upper 55% in gastrointestinal neuroendocrine carcinoma [8]. In our study, overall response rate to platinum-based therapy in ki67 levels below 55% was 53.8%, in ki 67 equal or over 55% was 79.2%. There was only one complete response in our study and this patient had ki 67 over 55%. These findings support the previous studies.

Limitations

There were some limitations in our study. These are retrospective nature and small number of patients.

Conclusion

Extrapulmonary neuroendocrine carcinomas have an aggressive behavior. Most of the patients respond to platinum-based therapy. Liver metastasis is a poor prognostic factor for progression-free survival.

Scientific Responsibility Statement

Statement The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal And Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict Of Interest

The authors declare no conflict of interest.

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